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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	34

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/197,056	RUSSELL ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 5-20-03, paper number 33, have been fully considered but they are not persuasive. Claims 21-40 have been canceled. Claims 41-48 have been added and are under consideration in the instant office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 41-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrases "delaying maximum polypeptide expression" and "the concentration of an inducing agent to which said cell is exposed" and "said increase in expression of said polypeptide occurring at a time after said introducing step" are new matter.

The phrase "obtaining a mammal that exhibits an immune response against a polypeptide" does not have support in the specification as originally filed which only suggested administering cells to a mammal that has already made an immune response to the immunogenic polypeptide. The breadth of obtaining any mammal that exhibits an immune response as new claimed is different and wider than administering a vector encoding an immunogenic polypeptide to a mammal that has already made an immune response to the immunogenic polypeptide.

2. Claims 41-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising a) transfecting a cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter *in vitro*, and b) increasing expression of the protein using tetracycline *in vitro*, does not reasonably provide enablement for administering the cells to a mammal that has had an immune response against the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 41-48 require increasing expression of a protein in a cell after it has been administered into a mammal, wherein said mammal has had an immune response against said protein prior to administering the cells. The only disclosed purpose for such methods is for therapy (e.g. pg 2, line 12, "cancer therapy"; pg 3, lines 21-23, "leukocytes that elicit an anti-tumor effect"; pg 8, line 24, "therapeutic (immunogenic) protein").

However, the combination of vector, promoter, level of expression, target tissue, dosage and route of administration required to obtain a therapeutic effect using gene therapy were unpredictable at the time of filing (Ross of record, 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1786, col. 1, para. 2, pg 1786, col. 1, para. 2; Verma of record, Sept. 18, 1997, Nature, Vol. 389, pg 239-242, see pg 239, 3rd col., line 10, pg 239, col. 1, line 16) for reasons of record.

To further support the unpredictability of the combination of elements required to obtain a therapeutic effect using gene therapy, the following references are provided: Miller of record

(1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Crystal of record (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification demonstrates transfecting Jurkat cells with a vector encoding a chimeric T-cell receptor (TCR) operably linked to the tetracycline operator and encoding tTA. The expression of the TCR is increased by decreasing the concentration of tetracycline *in vitro* (page 31). The specification does not teach administering cells to a mammal, regulating protein expression in a mammal, obtaining a therapeutic effect, how to use cells expressing TCR *in vivo*, how to increase expression of the TCR after the cells have been administered to a mammal, why

such cells would be administered to a mammal having an immune response against the TCR. The specification does not correlate the cells expressing TCR to cells expressing a protein that could be therapeutic in a mammal that has had an immune response to the protein. Overall, the specification does not overcome the unpredictability in the art by teaching the level of expression, route of administration, vector, promoter or cells required to obtain a therapeutic effect. Given the guidance provided in the specification taken with the unpredictability in the art, it would have required one of skill in the art undue experimentation to determine the parameters required to obtain a therapeutic effect using the method claimed.

Applicants argue the claims do not require obtaining a therapeutic effect. Applicants argument is not persuasive. Merely increasing expression of a protein in the absence of therapeutic effect does not have a disclosed use in a mammal having an immune response to the protein prior to administering the cell. The only disclosed purpose for the method claimed is for therapy (e.g. pg 2, line 12, "cancer therapy"; pg 3, lines 21-23, "leukocytes that elicit an anti-tumor effect"; pg 8, line 24, "therapeutic (immunogenic) protein"; pg 20, therapeutic genes).

Applicants argue it would not require one of skill undue experimentation to carry out the claimed method whether or not therapy was required. Applicants point out that a mammal having an immune response to an antigen could be obtained and the cells having a vector as claimed are adequately taught on pg 16, line 26, through pg 18, line 14 and pg 10, line 9, through pg 16, line 24. Applicants have essentially pointed to pg 10, line 9, through pg 18, line 14, as support for enablement. Applicants arguments are not persuasive. First, the argument is not

specific because applicants have not specifically discussed how pages 10-18 of the specification enable one of skill to obtain a therapeutic effect. Second, the basis of the rejection is that the combination of elements required to obtain the desired effect *in vivo* was not within the realm of routine experimentation. The specification does not overcome the art established unpredictability of gene therapy by teaching the level of expression, route of administration, vector, promoter or cells required to obtain a therapeutic effect. Pg 16, line 26, through pg 18, line 14 teaches how to make cells encoding a protein operably linked to a promoter; however, the basis of the rejection is not how to make the cells; it is how to used the cells to obtain a therapeutic effect. Pg 17, lines 14-29, for example teaches how to make a lymphocyte transfected with a vector encoding a T-cell receptor operably linked to a regulatable promoter. However, it cannot be determined how to use such a cell for therapy upon being introduced into a host. Pg 10, line 9, through pg 16, line 24, teach regulatable promoter systems but does not teach the combination of elements required to treat a patient. For example, pg 15, lines 14-21, teach a vector encoding GM-CSF under the control of a tet promoter; however, it cannot be determined how to use such a vector for therapy or why one would obtain a mammal having "an immune response against a polypeptide" such as GM-CSF and administer a vector encoding GM-CSF to such an mammal. Third, the specification does not teach how to regulate protein expression *in vivo*. The specification does not provide adequate guidance to regulate protein expression *in vivo* or to determine the combination of elements required to use the method claimed to obtain a therapeutic effect.

3. Claims 41-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 is indefinite because the phrase "delaying maximum polypeptide expression" is unclear. The maximum expression of a protein in a cell cannot be determined if expression is being inhibited. Therefore, it cannot be determined if the maximum has been delayed. Further, the maximum expression of a protein is a relative term. Under different conditions, such as temperature, CO2 levels, media, host tissue, etc., the maximum expression of protein would vary.

Claim 41 is indefinite because the phrase "wherein expression of said polypeptide by said cell is substantially inhibited *in vitro*" is confusing. The cell of step b) is not necessarily *in vitro*, in which case, expression of said polypeptide cannot be inhibited *in vitro*. Deletion of the phrase would overcome this rejection.

Claim 41 is indefinite because the metes and bounds of what applicants consider "substantially inhibited" cannot be determined. The phrase does not have an art accepted meaning and is not defined in the specification.

Claim 41 is indefinite because it does not clearly set forth that the mammal has an immune response against the protein prior to the step of introducing the cell into the mammal. While step a) must occur, the claim does not require step a) must occur prior to introducing the cell into the mammal.

Claim 41 is indefinite because step d) is unclear. The "regulatable promoter" and the inducing agent do not have a nexus. Nor is the increase in expression (step d) necessarily a result of regulation of the "regulatable promoter." The claim should clearly set forth that the cell comprises a vector encoding a protein operably linked to a drug-regulatable promoter and that expression is increased as a result of altering the amount of regulatory drug to which the cell is exposed (pg 4, lines 10-15).

Claim Rejections - 35 USC § 102

The rejection of claims 29-40, directed toward an isolated cell and a composition comprising a plurality of isolated cells, under 35 U.S.C. 102(a) as being anticipated by Cooke of record (Feb. 1997, J. General Virol., Vol. 78, pages 381-392) has been withdrawn because the claims have been canceled.

The rejection of claims 29-40, directed toward an isolated cell and a composition comprising a plurality of isolated cells, are rejected under 35 U.S.C. 102(b) as being anticipated by Knaus (July 1996, Mol. Cell. Biology, Vol. 16, pg 3480-3489) has been withdrawn because the claims have been canceled.

Claims 41-48 appear to be free of the prior art of record because the prior art of record did not teach a method comprising i) obtaining a mammal that exhibits an immune response against a protein, ii) obtaining cells comprising a vector comprising a regulatable promoter operably

linked to a nucleic acid sequence encoding said protein, iii) introducing cells to a mammal, and iv) increasing/decreasing the concentration of an inducing agent to the cells are exposed thereby causing an increase in expression of said protein.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson